REMARKS

Claims 38, 40, 41, 43, 45, 46, 49, and 65-68 are pending and stand rejected under 35 U.S.C. 112, first paragraph. Claims 39, 42, 44, 47, 48, 50, and 69-79 have been canceled. Applicants gratefully acknowledge withdrawal of the rejections under 35 U.S.C. 112, second paragraph.

The remaining rejections are believed to be overcome by the declaratory evidence attached hereto and are otherwise traversed for reasons discussed below.

35 U.S.C. §112, First Paragraph, Written Description

In the parent case, the Office rejected pending claims 38 and 65-68 on the grounds that Applicants' disclosure did not teach the structure and identifying characteristic features of the claimed transgenic mouse. (See, Final Office Action mailed September 13, 2001 in parent application 09/464,795).

Determining whether the written description requirement is satisfied is a question of fact. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *Regents of University of California v. Eli Lilly* 43 USPQ2d 1398 (Fed. Cir. 1997). The burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. Indeed, there is a strong presumption that an adequate written description is present when the application is filed. (See, *e.g.*, Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099, citing *In re Wertheim*, 191 USPQ 90 (CCPA 1976)). The Guidelines continue:

> The description need only describe in detail that which is new or not conventional. This is equally true whether the claimed invention is a product or a process. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics. (Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099).

Simply put, an applicant need only show that the parent disclosure conveys to one of skill in the art that they were in possession of the claimed invention at the time of filing. *In re Wertheim*, 191 USPQ 90 (CCPA 1976). There is no requirement that

structure (in terms of particular DNA nucleotide sequences) be recited in claims directed to transgenic animals.

Applying these rules to the instant application, Applicants submit that the specification as filed fully satisfies these written description requirements. Because Applicants are not claiming any and all transgenic mice, the specification is not required to exemplify or even to generally disclose any and all transgenic mice. Rather, all that is required is that Applicants show the application reasonably conveys to one of skill in the art that they were in possession of a transgenic mouse as recited in claims 38 and 65-68, *i.e.* a mouse containing control elements obtained from at least two stress-inducible genes operably linked to a sequence encoding a light-generating protein. Indeed, the specification clearly describes such expression cassettes and transgenic mice containing these expression cassettes. A myriad of representative species of stress-inducible control elements are described, for example, on pages 35-41. The particular structure of these control elements is also described in the references clearly delineated in these pages. In addition to disclosing a host of representative species of suitable control elements (and their structure), the specification also describes relevant, identifying characteristics of these control elements, for example, by relevant characteristics including but not limited to by their response to particular stressors. Similarly, representative examples along with structure and characteristics of light-generating protein are described. (See, *e.g.*, Section 3.2.0 of the specification).

Furthermore, the specification describes clearly how to make and test for transgenic mice as claimed. (See, *e.g.*, Section 4.0.0 of the specification and references cited therein). One of skill in the art would readily know if transgenic mice had been produced by simple testing procedures known in the art (*e.g.*, PCR, Southern blotting, Northern blotting, *in situ* hybridization, etc.) to determine if the sequences of the expression cassette have been integrated into the animal. It is entirely irrelevant -- both the description inquiry per se and to the practice of the invention -- where the sequences have integrated in the genome. Simply put, the structure and identifying characteristics of the claimed transgenic mice is whether or not they contain the claimed panel of expression cassettes. As detailed above, ample structure (sequence of these control elements as disclosed in cited publications) and identifying characteristics (*e.g.*, response to particular stimuli) of the claimed mice are provided so that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

Applicants also remind the Examiner that affidavits by experts and references to patents and publications available to the public at the filing date of the application can be

used to establish what the specification reasonably conveys to the skilled artisan. *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). Further, the Office must articulate adequate reasons to rebut a Declaration that properly used facts to arrive at a logically reasoned conclusion (see, *In re Alton, supra*). Further evidence establishing that the specification satisfies the description requirement of Section 112 is presented herewith in the form of a Rule 132 Declaration by Dr. David West:

> 6. When the specification was filed, it clearly conveyed to a typical scientist that the inventors had in their possession the invention of the claims (as set forth in paragraph 4, above). By "in their possession," I mean that the inventors contemplated transgenic mice comprising a panel of expression cassettes, wherein the panel comprises at least two different expression cassettes, each having a different stress-inducible control element operably linked to sequence encoding a light-generating polypeptide, and that they had, using the specification and information available to a typical scientist, a practical way of making and using such transgenic mice. Thus, I believe that a typical scientist would have understood the specification clearly described all of the various aspects of the claims and enabled a typical scientist to make and use the invention as set forth in the pending claims. I base this belief on the facts set forth below.
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> 7. First, at the time the specification was filed, it was widely known how to construct expression cassettes generally. ...
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> 8. Second, it would have been clear to a typical scientist that the inventors had in their possession the various polynucleotide components of the expression cassettes. ...
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> 9. Third, it would have been plain to a typical scientist from the specification that the inventors were in possession of an operative way of making the claimed transgenic mice. The specification describes methods of making transgenic animals on page 59, line 28 to page 60, line 8 and in the references cited therein. At the time the application was originally filed, such methods were routine to the typical scientist. Indeed, methods of introducing multiple expression constructs, each with their own separate promoter, to create transgenic founders are described in the art. (See, *e.g.,* Jankowsky et al. (2001) *Biomol Eng* 17(6):157-165, copy of the Abstract attached hereto). Also routine at the time of filing were methods of assaying if a sequence from an expression cassette had been integrated into a host mouse's genome and, if so, where such integration occurred. Such assay methods include, but are not limited to, PCR, Northern and/or Southern blotting (for example of particular tissues) as well as *in situ* hybridization and/or imaging techniques.
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> 10. Fourth, a typical scientist would have known that the inventors were in possession of operative methods of using these

transgenic mice, for example, to determine the effect of an analyte. The evaluation of whole transgenic animals having light-reporter systems is described on line 29, page 60 through line 6, page 61 of the specification.

...

13. Therefore, taken as whole, the specification unambiguously conveyed to a typical scientist that the inventors contemplated including a panel of expression cassettes in a transgenic mouse comprising the stress-inducible control element operably linked to light-generating polypeptide-encoding sequence as disclosed in the specification. The inventors also had in their possession an operative way of using these transgenic animals to evaluate the effect of analyte in a whole animal. In sum, based on the disclosure of the specification and the level of knowledge of a typical scientist regarding expression cassettes, transgenic animals and assays for integration available at the time of filing, I believe that the specification as filed clearly conveys that the applicants had invented the expression cassettes and methods as set forth in the claims.

In view of the above amendments and arguments, Applicants submit that the claims comply with the requirements of 35 U.S.C. §112, first paragraph. Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

35 U.S.C. §112, First Paragraph, Enablement

In the parent case, the Examiner asserted that undue experimentation would be required in order to practice the invention of claims 38, 40, 41, 43, 45, 46, 49 and 65-68. Repeatedly the Examiner asserts that the specification is not enabling for producing "any and all transgenic animals comprising more than one expression construct because the specification does not provide sufficient guidance, evidence, and working examples to make all the transgenic animals and because the art of making transgenic animals is highly unpredictable." (e.g., Final Office action, page 4, first paragraph).

Applicants submit that the evidence of record establishes that the claims as pending are fully enabled by the specification as filed.

The specification fully enables the pending claims

It is well settled that the enablement requirement is satisfied if the applicant's specification teaches one of skill in the art how to make and use the claimed invention without undue experimentation. *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988). When determining whether the amount of testing required is "undue", the courts have

determined that "time and difficulty of experiments are not determinative if they are merely routine." (see, *e.g., In re Wands,* 8 USPQ2d at 1404, citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976). In fact, in *United States v. Telectronics Inc.,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989), the Federal Circuit ruled that a specification setting forth one working embodiment and a method of testing other embodiments was enabling, even in the face of evidence that testing for other suitable embodiments would require approximately $50,000 and 6-12 months. (see, also, USPTO Training Manuals on Enablement, page 31).

Furthermore, one does not look to the claims, but to the specification to find out how to practice the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.* 220 USPQ 303 (Fed. Cir. 1983). Proof of enablement is required only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole. In addition, the scope of enablement must bear only a reasonable (not exact) correlation to the scope of the claims. *See, e.g., In re Fisher,* 166 USPQ 18 (CCPA 1970) and M.P.E.P. 2164.08. Simply put, it is not required that Applicants exemplify each and every possible transgenic animal for each and every stress-inducible control element in order to satisfy the enablement requirement.

The specification itself, along with the state of the art at the time of filing, strongly belie the Examiner's position. With regard to the generation of transgenic animals, Applicants note that the practice of making such animals was utterly routine at the time of filing. (See, *e.g.,*. page 59, line 28 to page 60, line 7 of the specification and patents referenced therein). Similarly, the use of light-reporter systems in whole animals is also fully enabled by the specification. (See, *e.g.,* Section 4.2.0 of the specification starting on page 70; and United States Patent 6,217,847, by Contag, et al., issued April 17, 2001, filed January 19, 1999 (this patent is a divisional of co-owned U.S. patent application Ser. No. 08/602,396, filed Feb. 16, 1996, now abandoned, which is continuation-in-part of co-owned U.S. patent application Ser. No. 08/270,631, filed Jul. 1, 1994, now U.S. Patent No. 5,650,135, a copy of which was previous submitted). Thus, the Office has not met its burden of showing the specification as filed does not enable the invention as set forth in the claims.

Despite the failure of the Office to make a case for non-enablement, Applicants again address why the claims, as pending, are enabled throughout their scope. As previously discussed, enablement is fact-dependent. The standards articulated in *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988) are used to help determine whether the specification at issue is in fact enabling. Indeed, the situation in *Wands* is highly

analogous to that at hand. In *Wands,* the Federal Circuit held that claims to generic monoclonal antibodies were enabled by a specification that taught the entire procedure of making monoclonal antibodies. Moreover, in view of the high level of skill in the art and routine nature of each step of the antibody-making procedure, the court held that the amount of experimentation required to make other monoclonals was extensive, but not undue.

Similarly, in the pending case, in view of the high level of skill in the art and routine nature of each step of making transgenic animals (and imaging these animals), experimentation would not be undue. Applicants have repeatedly pointed out that their specification clearly sets forth the procedure for identifying and making expression cassettes which in turn introduce (randomly or site-specifically) polynucleotides into a mouse, thereby creating a transgenic mouse as claimed. One skilled in the art (*e.g.,* a PhD in molecular biology) could readily practice these procedures. Thus, Applicants again traverse the Office's assertion that there was a lack of predictability regarding the generation of transgenic animals or the ability to image these animals at the time of filing. Indeed, when the factors in *Wands* are weighed, it would not require undue experimentation to practice the claimed invention, given the guidance found in the specification and state of the art.

In addition, to further rebut any argument that using the claimed methods is "unpredictable" or would require "undue experimentation," Applicants submit herewith evidence documenting that, using the methods set forth in the specification, a skilled artisan could readily practice the claimed invention throughout its scope. In this regard, Exhibit A (an abstract by Jankowsky et al. published after Applicants' priority date) establishes that multiple, separate expression constructs can be used to create transgenic mice and, indeed, that separate constructs are seemingly superior to bicistronic constructs. (See, Exhibit A and paragraph 9 of the attached Rule 132 Declaration). In addition, the Dr. David West's Declaration, submitted pursuant to Rule 132, states:

> 10. It is also my opinion that applying these methods of evaluation to the claimed transgenic mice and methods of using these mice would have been routine to one working in this area in view of Applicants teachings.
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> 11. It is further my opinion that one skilled in the art would understand from the specification that the claimed transgenic mice could be made using techniques described in the specification or known at the time of filing. (See, *e.g.,* page 59, line 28 to page 60, line 8). Further, the specification discusses how to prepare transgenic animals and how to

performing imaging experiments on these animals, etc. Thus, I believe that, based on the application and level of skill in the art, one working in this field would be able to make and use the claimed transgenic mice. ...

13. Therefore, taken as whole, the specification unambiguously conveyed to a typical scientist that the inventors contemplated including a panel of expression cassettes in a transgenic mouse comprising the stress-inducible control element operably linked to light-generating polypeptide-encoding sequence as disclosed in the specification. The inventors also had in their possession an operative way of using these transgenic animals to evaluate the effect of analyte in a whole animal. In sum, based on the disclosure of the specification and the level of knowledge of a typical scientist regarding expression cassettes, transgenic animals and assays for integration available at the time of filing, I believe that the specification as filed clearly conveys that the applicants had invented the expression cassettes and methods as set forth in the claims.

The Cited References do not Establish Unpredictability

Applicants also disagree with the assertion that certain references demonstrate the unpredictability of making trangenic mice. (Final Office Action, pages 4-5). The Examiner cites Cameron and Cui in support of the notion that "unless a transgenic mouse has been produced, one cannot predict what will the characteristics of the transgenic mouse comprising a panel of expression constructs and thereof, an artisan would not know how to use the claimed transgenic mouse in claimed methods." (Final Office Action, sentence bridging pages 6 and 7).

Applicants remind the Examiner that the standard of enablement is not, and never has been, actually production of the claimed composition. Rather, the specification is presumed enabling as filed and the burden is on the Examiner is to provide evidence as to why a skilled artisan could not make or use the claimed invention based on the guidance of the specification. Thus, the Office must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the Office must prove the disclosure requires undue experimentation. *In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971).

Applicants submit that, in the pending case, the Office has failed to provide adequate evidence to support the present enablement rejection. Indeed, Applicants note that the parent application (from which the present application is derived) was filed more than 5 years after Cui published and more than 2 after Cameron published. Therefore, the cited references are not an appropriate indicator regarding the state of the art of

transgenic mice at the time the present application was filed. The field of transgenic mice is undergoing constant and rapid changes and, indeed, patents directed to methods of making and using such animals have been issued by the Office both before and since the publication of Cameron and Cui. As such, the Office has failed to provide adequate evidence to support the present rejection and, accordingly, the rejection cannot be sustained.

Even assuming, for the sake of argument only, that Cameron and Cui were relevant to the issue of enablement in the pending case, Applicants submit that the specification fully enables the claims throughout their scope. In fact, it is axiomatic that the scope of an applicant's claims is not limited to those embodiments that are actually exemplified in the specification. (*see, e.g., Spectra-Physics Inc. v. Coherent Inc.,* 3 USPQ2d 1737 (Fed. Cir. 1988)). Rather, the test is whether one skilled in the art, in view of the state of the art at the time of filing, could practice the invention without undue experimentation. *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988).

Applying these standards to the case at hand, Applicants submit that their specification enables the pending claims throughout their scope and that the references do nothing to undermine this fact. As a threshold matter, Applicants again note the characteristics of the claimed transgenic mouse can be readily assayed by one of skill in the art. (See, discussion in above section regarding standard techniques such as PCR, blotting, FISH, etc.). Moreover, the references cited by the Examiner do nothing to support the allegation of unpredictability. Cameron is a review article primarily addressing production of transgenic livestock. (See, Cameron, Abstract). Section 4 of this article, cited by the Examiner on page 4 of the Final Office Action includes not only a discussion regarding position effects but, in addition, discussions relating to (1) how to overcome such effects (See, Section 4.1) and (2) to how to assay transgenic expression (See, Section 4.2). Similarly, Cui is entirely irrelevant to the claimed invention as it does not even mention the use of light-generating polypeptides as *in situ* reporters. (See, Cui page 183). Since the cited references are not relevant to the claimed invention, there is no evidence in these references that establishes unpredictability of the claimed invention.

Further evidence regarding enablement is submitted herewith. First, attached hereto is Jankowsky et al. (2001) *Biomol Eng* 17:157-165. This article compares mice into which multiple transgenes have been introduced and concludes that copy number and expression is superior when the transgenes are introduced using separate constructs (rather than bicistronic lines). This article demonstrates that one of skill in the art could

have followed the teachings of the specification to make and use the claimed transgenic mice having a panel of expression cassettes.

Second, Applicants submit herewith a Rule 132 Declaration in which it is stated:

> 12. It is further my opinion that Cameron and Cui are not relevant to the subject matter claimed in the application. Cameron is directed primarily to transgenic livestock. (See, Cameron, Abstract). Further, the issues raised in Cameron regarding poor levels of expression are not relevant to the claimed invention for a variety of reasons. First, transgenic mice containing the claimed expression cassettes can be readily assayed for expression levels and only those animals exhibiting the desired expression levels can be used. (See, also, paragraph 9 above). Second, leaky expression is not a major issue in the practice of the present invention -- where the expression cassettes integrate is irrelevant so long as expression of the light-generating protein is inducible via a stress-inducible control element. (See, also, paragraph 9 above). For its part, Cui is not relevant to the claimed invention because it is not directed to the use of light-generating proteins as *in situ* reporters. (See, Cui, page 183). Thus, I believe that one working in this field would have no reason to apply this information to the claimed invention. Accordingly, I do not believe that Cameron or Cui to be relevant to the claimed invention.

Thus, as the evidence of record makes clear, the teachings of the specification are more than sufficient to enable one of skill in the art to practice the claimed invention. Applicants respectfully request that the rejection of the claims under 35 U.S.C 112, first paragraph, be withdrawn.

CONCLUSION

Applicant respectfully submits that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 325-7812.

Respectfully submitted,

Date: June 11, 2002 By: Dasternak

Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicants

ROBINS & PASTERNAK LLP
545 Middlefield Road, Suite 180
Menlo Park, CA 94025
Tel. 650-325-7812
Fax. 650-325-7823

Currently Pending Claims

38. (Amended) A transgenic mouse comprising a panel of expression cassettes, said panel comprising

a first expression cassette comprising a first control element derived from a first stress-inducible gene, said control element operably linked to sequences encoding a first light generating polypeptide, and

a second expression cassette comprising a second control element derived from a second stress-inducible gene, said second control element operably linked to sequences encoding a second light generating polypeptide,

wherein said expression cassettes have been introduced into said transgenic mouse or an ancestor of said transgenic mouse, at an embryonic stage.

40. (Amended) A method of determining the effect of an analyte on gene expression mediated by control elements derived from stress-inducible genes, wherein said expression is in a living transgenic mouse, said method comprising

administering the analyte to a living transgenic mouse of claim 38, wherein administering of said analyte is carried out under conditions that permit light generation mediated by said light generating polypeptide in the transgenic mouse,

determining the effect of the analyte on expression of the light generating polypeptide in a living transgenic mouse wherein said expression is mediated by at least one of the control elements.

41. (Amended) The method of claim 40, wherein said conditions that permit light generation mediated by the light generating polypeptide includes administering, to the transgenic mouse, at least one substrate for the light generating polypeptide.

43. (Amended) The method of claim 40, wherein the expression cassettes of said transgenic mouse comprise control elements derived from stress-inducible genes, and said analyte is screened for its affect on expression of stress-inducible genes.

45. (Amended) A noninvasive method for detecting a level of expression in response to an analyte, wherein said expression is (i) mediated by control elements derived from stress-inducible genes, and (ii) in a living transgenic mouse, said method comprising

(a) administering the analyte to a living transgenic mouse of claim 38, wherein administering of said analyte is carried out under conditions that permit light generation mediated by said light generating polypeptide,

(b) placing the transgenic mouse within a detection field of a photo detector device,

(c) maintaining the transgenic mouse in the detection field of the device, and

(d) during said maintaining, measuring photon emission from the transgenic mouse with the photo detector device to detect the level of expression of the light generating polypeptide in the living transgenic mouse wherein said expression is mediated by at least one of the control elements.

46. (Amended) The method of claim 45, further comprising,

(e) repeating steps (b) through (d) at selected intervals, wherein said repeating is effective to detect changes in the level of the light emission in the transgenic mouse over time.

49. (Amended) A method of providing a transgenic mouse suitable for screening a selected analyte, comprising

generating a transgenic mouse of claim 38, and

providing said transgenic mouse or progeny thereof for use in screening a selected analyte.

65. (Amended) The transgenic mouse of claim 38, said panel further comprising

a third expression cassette comprising a control element derived from a third stress-inducible gene, said third control element operably linked to sequences encoding a third light generating polypeptide.

66. (Amended) The transgenic mouse of claim 65, wherein (i) said first, second, and third control elements are each derived from a different gene, and (ii) said first, second, and third light generating polypeptides produce the same color of light.

67. (Amended) The transgenic mouse of claim 65, wherein (i) said first, second, and third control elements are each derived from a different gene, and (ii) at least two of said first, second, and third light generating polypeptides produce different colors of light.

68. (Amended) transgenic mouse of claim 65, said panel further comprising additional expression cassettes, wherein each expression cassette comprises a control element derived from a different stress-inducible gene, said control element operably linked to sequences encoding a light generating polypeptide.